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ATTORNEY DOCKET NO. 10011076-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Robert Kincaid

Serial No.: 10/087.035

Examiner: Carolyn L. Smith

Filing Date: February 27, 2002

Group Art Unit: 1631

Title: ARRAY DESIGHN SYSTEM AND METHODS

COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria VA 22313-1450

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TRANSMITTAL OF APPEAL BRIEF Sir: Transmitted herewith is the Appeal Brief in this application with respect to the Notice of Appeal filed on April 27, 2007 The fee for filing this Appeal Brief is (37 CFR 1.17(c)) \$500.00. (complete (a) or (b) as applicable) The proceedings herein are for a patent application and the provisions of 37 CFR 1.136(a) apply. (a) Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17(a)(1)-(5)) for the total number of months checked below: one month \$ 120.00 two months \$ 450.00 three months \$1020.00 four months \$1590.00 The extension fee has already been filled in this application. (b) Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time. Please charge to Deposit Account 50-1078 the sum of \$500.00 . At any time during the pendency of this application, please charge any fees required or credit any overpayment to Deposit Account 50-1078 pursuant to 37 CFR 1.25. A duplicate copy of this transmittal letter is enclosed. Respectfully submitted, Express Mail No. EV 954 013 090 US k hereby certify that this correspondence is being deposited Robert Kincaid with the United States Postal Service A THE STATE OF THE INC. an envelope addressed to: Commissioner for Patents, Βv P.O. Box 1450, Alexandria, VA 22313-1450. Bret E. Field for John Brady Date of Deposit: June 26, 2007 Attorney/Agent for Applicant(s) I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below. Reg. No. 37,620 Date of Facsimile: Date: June 26, 2007 Typed Name: Saundra 🔊 Hunter Telephone No. (650) 327-3400



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First Named Inventor	Kincaid, Robert
Examiner	Smith, Carolyn L.
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Title: Array design system and methods

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated November 29, 2006. No claims have been allowed, and Claims 1-11, 22, 27, 28, 31-37, 41-44 and 46-49 are pending. Claims 1-11, 22, 27, 28, 31-37, 41-44 and 46-49 are appealed. A Notice of Appeal was filed on April 27, 2007, making this Brief due by June 27, 2007. Accordingly, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

Provided herewith is an authorization to charge the amount of \$250.00 to cover the fee required under 37 C.F.R. §41.20(b)(2) for filing Appellants' Brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-1078, reference no. 10011076-1.

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REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights to the invention to Agilent Technologies. Inc.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on February 22, 2002, with Claims 1 to 30. During the course of prosecution, Claims 31 to 49 were added, Claims 12-21, 23-26, 29, 30, 38-40, and 45 were canceled. Accordingly, Claims 1-11, 22, 27, 28, 31-37, 41-44, and 46-49 are pending in the present application. All of the pending claims stand rejected and are appealed herein.

STATUS OF AMENDMENTS

The amendments to the Claims filed subsequent to issuance of the Final Rejection were entered by the Examiner.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to systems and methods for array design that allow users or customers of arrays to input various selectable array design parameters that are usable by a specialized array designer or vendor for preparation of completed array designs or fabricated array chips. The systems and methods of the invention permit decoupling of computation-intensive aspects of array design from simpler aspects of the design process. The level of array parameter input by customers can be varied according to the interests and sophistication level of the individual customers.

Below is a description of each appealed independent claim and where support for each can be found in the specification.

Independent Claim 1 claims a method for array design, including the steps of: (a) selecting, by a customer, at least one array design parameter and at least one gene of interest (see, e.g., page 3, lines 21-24); (b) providing the at least one customer selected array design parameter and the at least one gene of interest to a vendor (see, e.g., page 3, lines 24-25); (c) curating, by the vendor, a sequence for said at least one gene of interest(see, e.g., page 4, lines 1-2); (d) selecting, by the vendor, at least one probe specific for the curated sequence (see, e.g., page 4 lines 2-3); (e) providing, by the vendor, at least one additional array design parameter (see, e.g., page 3 lines 3-4); and (f) completing at least one array design using the at least one customer selected array design parameter, the at least one vendor selected probe, and the at least one vendor provided array design parameter (see, e.g., page 3 lines 1-5).

Independent Claim 22 claims a gene-based array design system that includes: (a) means for selecting, by an array customer, at least one gene of interest (see, e.g., page 10, lines 11 to page 11 line 8, describing user computers 12 and programming 14); (b) means for providing the at least one customer selected gene of interest to a vendor (see, e.g., page 11, line 10 to page 12, line 10; describing vendor server 16 with programming 18 in communication with user computer 12 with programming 14); (c) means for curating, by the vendor, sequence information for the at least one customer selected gene of interest (see, e.g., page 15, lines 10-18; describing programming 30a on vendor computer 26a for curation of sequences); (d) means for selecting, by the vendor, a plurality of nucleic acid probes specific for the customer selected gene of interest (see, e.g., page 15, lines 10-18; describing programming 30b on vendor computer 26b for probe selection); and (e) means for completing at least one array design that includes at least one of the vendor selected nucleic acid probes specific for the customer selected gene of interest(see, e.g., page 15, lines 10-18; describing programming 30n on vendor computer 26n for completing array design).

Independent Claim 27 claims a method for gene-based array design including the steps of: (a) selecting, by a customer, at least one gene of interest (see, e.g., page 3, lines 21-24); (b) providing the at least one customer selected gene of interest to a vendor (see, e.g., page 3, lines 24-25; and page 3, line 32 to

page 4, line 3); (c) curating, by the vendor, sequence information for the at least one customer selected gene of interest (see, e.g., page 4, lines 1-3); (d) selecting, by the vendor, a plurality of nucleic acid probes specific for the at least one customer selected gene of interest (see, e.g., page 4 lines 2-3); and (e) completing at least one array design that includes at least one of the vendor selected nucleic acid probes specific for the at least one customer selected gene of interest (see, e.g., page 3 lines 1-5).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

- I. Claims 1-22, 22, 27-28, 31-37, 41-46 and 48 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Zhou et al. (US 2003/0120432).
- II. Claims 47and 49 are rejected under 35 U.S.C. § 103 as being unpatentable over Zhou et al. (US 2003/0120432) in view of Rothberg et al. (2003/0003463).

ARGUMENT

I. Claims 1-22, 22, 27-28, 31-37, 41-46 and 48 are not anticipated under 35 U.S.C. § 102(e) over Zhou et al. (US 2003/0120432).

The Appellants will argue the Claims in the following groups: Claims 1, 2, 4-11, 22, 27, 28, 31, 33-37, and 41 as a first group; Claims 3 and 32 as a second group; and Claims 42-44, 46 and 48 as a third group.

The standard for anticipation under 35 U.S.C. § 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Further, an anticipatory reference must be enabling so as to place one of ordinary skill in possession of the claimed invention, *Akzo N.V. v. United States Int'l Trade Comm'n* 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), *cert denied*, 482 U.S. 909 (1987). To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.* 334 U.S. P.Q.2d 1565 (Fed. Cir. 1995).

As set forth in the arguments below, the Appellants contend that the reference cited by the Examiner fails to teach each and every element of the claimed invention, and as such does not anticipate it.

Zhou et al. Priority Claim

The subject application was filed on February 27, 2002. The reference cited by the Examiner in making this rejection is U.S. Patent Publication No. 2003/0120432, filed on November 26, 2002. The filing date is thus nine months after the filing date of the subject application. As such, the Examiner has relied upon previously filed provisional applications to which Zhou et al. claims priority in making this rejection.

On January 21, 2005, the Appellants provided a Declaration of Robert Kincaid (the inventor) under 37 C.F.R. §1.131 which provides a showing of facts that the inventor conceived of the claimed invention prior to the July 16, 2001 (provided as Exhibit A in the Evidence Appendix of this Appeal Brief). In view of this Declaration, only the content of provisional applications cited in Zhou et al. that were filed prior to July 16, 2001 can be considered to assess anticipation of the claimed invention by Zhou et al. Only provisional applications 60/265,103 (the '103 provisional), filed on January 29, 2001, and 60/301,298 (the '298 provisional), filed on June 25, 2001, fall into this category.

Zhou et al. is a Continuation-in-part (CIP) of applications 10/063,559 and PCT/US02/13902, both filed May 2, 2002. Appellants note that the '103 provisional was filed more than 1 year before the filing of these parental applications. As such, the '103 provisional expired prior to the filing of the parental applications of Zhou et al. and thus cannot serve as a priority document to either Zhou et al. or its parental applications.

Based on these facts, the only priority document of Zhou et al. that currently qualifies as prior art to the subject application is the '298 provisional patent application. It is to this application that the Appellants are contrasting the subject claimed invention in the arguments below. During prosecution, the Appellants provided a copy of the '298 provisional application to the Examiner (on February 28, 2007). The '298 provisional application is provided as Exhibit B in the Evidence Appendix of this Appeal Brief.

In making the above conclusion regarding the applicability of the '298 provisional application as prior art to the subject application, the Appellants are not forfeiting their right to present a showing of facts in the future to establish that conception of the claimed invention antedates the '298 provisional application.

Group I: Claims 1, 2, 4-11, 22, 27, 28, 31, 33-37, 41 and 43

Claims 1, 22 and 27 are the only independent claims of the subject application. Claims 1 and 27 are drawn to drawn to methods for gene-based array design that includes selecting, by a customer, at least one gene of interest and providing this selection to the vendor. The customer may also provide additional array design parameters (in Claim 1), including probe design parameters and/or array layout design parameters. The vendor then curates sequence information for the gene(s) of interest and selects a plurality of probes specific for this curated sequence for the gene(s) of interest. The vendor provides additional array design parameters necessary for completing the array design. The parameters of array design now established, the array design is completed (either by the vendor or the customer). Independent Claim 22 is drawn to gene-based array design systems having means for completing an array design that includes means for curating sequence information for a customer selected gene of interest and means for selecting nucleic acid probes specific for the gene of interest.

Curating a sequence is described in the subject application on page 20, lines 11-19 (Paragraph [0071]), which reads as follows:

Event 140 also includes sub-event 160 wherein sequence curation is carried out. Sequence curation typically involves checking the raw sequences from event 150 for errors such as incorrect sequences and incorrect 5'-3' ordering of sequences. Sequence curation 160 may also include removal of commonly repeated subsequences such as ALU repeats and the like which would give rise to non-specific probes, and removal of any artifacts associated with sequence assembly, such as residual vector sequences. Various other methods of preparing sequences for probe selection will suggest themselves to those skilled in the art, and are considered to be within the scope of the invention.

As is clear from the section above, curation of a sequence involves "methods of

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preparing sequences for probe selection", with exemplary methods including checking raw sequences for errors, removal of commonly repeated sequences and artifact removal. As such, curation of sequences for genes of interest is performed prior to selection of probes for that sequence and, as described in the specification, is meant to increase the quality of probes selected.

Zhou et al. discloses methods for allowing a customer to provide specific parameters for a custom array design to a vendor which would be used in making a final custom array design. While a number of customer-provided array parameters are disclosed in Zhou et al., the Appellants contend that nowhere in the '298 provisional application is it taught that a vendor curate a sequence for a gene of interest identified by a user and then select probes for the curated sequence as is claimed.

The Examiner asserts that the '298 provisional application teaches curating sequences for a gene of interest and identifying probes for the curated sequence as is claimed. In support of this assertion, the Examiner has cited pages 2, 4 and 19 of the '298 application.

Page 4 of the '298 application shows a flow chart of the array design system. However, nowhere in this flow chart is curation, as described in the specification, shown.

On page 19 of the '298 provisional application under "Initial Offereings" (a section specifically called out by the Examiner), a list of catalog designs available are listed. This listing has nothing at all to do with curating a sequence.

On page 2 of the '298 provisional application, the term "Custom Design" is defined as "The design of an expression array based on sequences and instructions provided by a user". However, this brief description fails to provide any specifics regarding the identity of the "sequences" provided by the user or how they are processed in making an array design.

With regard to what "sequences" are provided by a user and how they are manipulated, the '298 application on pages 8-9 (starting under the heading "Login and Order" on page 8) states the following:

Login and Order

Once logged in, a user has two ways to start a design request. First, upload a file containing a list of desired probe sets (from past experiments and/or various searches performed using Affymetrix tools). If the file format is not correct, error(s) will be displayed. It will also show link to the file description for a Probe Set File. Once uploaded, the data in the file will be checked against FCdb. If a probe set cannot be located, it will be deleted from the list, and the user will be notified of the deletion. If a probe set can be located, but for a different design than the one indicated, the information will be shown to the user, and he/she may elect to add it to the list. If a probe set can be located in more than one design (using the probe set name as the only criterion), all designs with the same probe set name will be listed. Alternatively, if the user provides the same probe set name multiple times, this duplicated error will also show up. The user may elect just one set, or elect multiple sets by giving a distinct name to each set selected.

The second way is to perform a search and select the desirable probe sets returned by the query. The user must provide at least one criterion in order to search. When multiple criteria are selected, the query will search ALL or ANY of those criteria against FCdb. The query results will be displayed but not selected. The user may select one or more probe sets returned and add them to the design request.

As is clear from the above excerpt, a user may do one of two things to begin the array design process of the '298 provisional application: 1. upload a file containing a list of desired probe sets (or sequences); or 2. search the vendor database for existing probe sets and select the probe sets of interest returned by the query. Therefore, the "sequences" provided by the user are in the form of a list of probe sequences (i.e., probe sets) that are to be included in the desired array design. Nowhere in the '298 provisional application is it taught that the probe sets provided by a user are curated nor is it taught that additional probes are selected for these submitted probe sets (they are already probes to begin with).

Therefore, the Appellants submit that the '298 provisional application, the only priority document of Zhou et al. that currently qualifies as prior art to the subject application, fails to teach curating a sequence for a gene identified by a user as is claimed. Because the '298 provisional application does not teach each and every element of the claimed invention, the Appellants respectfully request reversal of the rejection of Claims 1, 2, 4, 6-11, 22, 27, 28, 31, 33-37, 41 and 43 as being anticipated

under 35 U.S.C. § 102(e) over Zhou et al.

Group II: Claims 3 and 32

Claim 3 depends from independent Claim 1 and Claim 32 depends from independent Claim 27 and further specify that the step of completing the array design is carried out by the user/customer.

Due to their dependency on Claims 1 and 27, Claims 3 and 32 are not anticipated by Zhou et al. (i.e., the '298 provisional application) for the reasons detailed above for the Claims of Group I.

In addition, the Appellants submit that nowhere in the '298 provisional application is it taught that an array design be completed by the user/customer. Indeed, the Examiner has failed to even assert that this element is taught in Zhou et al.

Therefore, because Zhou et al. fails to teach either curating a sequence for a gene identified by a user or that the array design be completer by the user, the Appellants respectfully request reversal of the rejection of Claims 3 and 32 as being anticipated under 35 U.S.C. § 102(e) over Zhou et al.

Group III: Claims 42-44, 46 and 48

Claims 42, 46, and 48 depend from Claim 1; Claim 43 depends from Claim 22 and Claim 44 depends from Claim 27. Claims 42, 43, 44 and 46 further include the limitation that the curating step includes checking the sequence for errors, removal of commonly repeated subsequences, and/or removal of any artifacts associated with sequence assembly. Claim 48 further includes the limitation that the curating step includes removal of commonly repeated subsequences.

Due to their dependency on one of Claims 1, 22 and 27, Claims 42-44 and 46 and 48 are not anticipated by Zhou et al. (i.e., the '298 provisional application) for the reasons detailed above for the Claims of Group I.

In addition, given that the '298 provisional application fails to teach a curating step at all (argued above for Group I), the Appellants submit that it clearly fails to teach a curating step that includes one or more of checking the sequence for errors, removal

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of commonly repeated subsequences, and removal of any artifacts associated with sequence assembly.

Therefore, because Zhou et al. fails to teach curating a sequence for a gene identified by a user that includes one or more of checking the sequence for errors, removal of commonly repeated subsequences, and removal of any artifacts associated with sequence assembly, the Appellants respectfully request reversal of the rejection of Claims 42-44, 46 and 48 as being anticipated under 35 U.S.C. § 102(e) over Zhou et al.

In summary, the Appellants submit that, for the reasons argued above, Zhou et al. fails to teach each and every element of Claims 1-22, 22, 27-28, 31-37, 41-46 and 48 of the claimed invention and therefore cannot anticipate these claims. Reversal of this rejection is thus respectfully requested.

II. Claims 47and 49 are not unpatentable under 35 U.S.C. § 103 over Zhou et al. (US 2003/0120432) in view of Rothberg et al. (2003/0003463).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992). Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986). Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

As set forth in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), the four factual inquires for determining obviousness are as follows:

- (A) Determining the scope and contents of the prior art;
- (B) Ascertaining the differences between the prior art and the claims in issue;

- (C) Resolving the level of ordinary skill in the pertinent art; and
- (D) Evaluating evidence of secondary considerations.

Recently, in KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (U.S. 2007), the Supreme Court reviewed the TSM test. While the Court warned against its "rigid application" (KSR, slip op. at 15), the Court also found that the TSM test could provide a "helpful insight" in determining whether the claimed subject matter is obvious under §103(a) (KSR, slip op. at 14).

With regard to the present rejection, the Appellants argue that the combined teaching so the cited references fail to teach or suggest each and every element of the claimed invention.

The Appellants will argue the Claims in the following groups: Claim 47 as a first Group and Claim 49 as a second Group.

The Examiner acknowledges that Zhou et al. fails to teach both checking for errors in a sequence for the gene of interest identified by a user (as claimed in Claim 47) and the removal of any artifacts associated with a sequence assembly for the gene of interest identified by a user (as claimed in Claim 49).

To remedy this deficiency, the Examiner cited Rothberg et al.

As argued below, the Appellants submit that Rothenberg et al. fails to remedy the deficiencies in the teachings of Zhou et al. because it does not teach or suggest the missing subject matter of Zhou et al.

Group I: Claim 47

As noted above, Claim 47 specifies that the curating step includes checking the sequence (for a gene identified by a user) for sequence errors. As described on page 20, lines 12 – 13, this checking step includes the identification of incorrect sequences in a sequence of interest or incorrect 5'-3' ordering of sequences. Identification of errors in a sequence informs the probe selection process, for example by preventing probes from being selected form regions of the sequence having errors. Checking the sequence for errors as claimed is not carried out during the course of using an array in a hybridization experiment, but rather is part of the array design process.

In rejecting Claim 47, the Examiner asserts that Rothberg et al. teaches error identification as claimed in Claim 47. To support this assertion, the Examiner cites Claim 51 and paragraphs [0069] and [0226] of Rothberg et al.

Claim 51 of rothberg et al. reads as follows:

- 51. A detection array for recognizing terminal subsequences of target nucleic acids, said array comprising:
 - (a) one or more surfaces;
 - (b) a plurality of discrete observational cells arranged on said surfaces in which are bound probe molecules, each

probe molecule being a member of one of a plurality of species of probe molecules, wherein each discrete observational cell has bound probe molecules of at most one species, and wherein said probe molecules comprise:

- (i) a hybridization region, wherein said hybridization region of said probe molecules of one species of probe molecule are capable of hybridizing with said terminal subsequences of said target nucleic acids having a single nucleotide sequence,
- (ii) a core region adjacent to and conjugated with said hybridization region, and
- (iii) an attachment means for binding said hybridization region and said core region to said surfaces; and
- (c) a plurality of discrete error-checking cells to which are bound probe molecules, wherein to each discrete errorchecking cell are bound probe molecules of a plurality of species, such that each species of probe molecule is bound to one discrete observational cell and to at least one discrete error-checking cell.

As is clear from above, the error identification of Claim 51 of Rothberg et al. (step c) is not drawn to identifying errors in the sequence as part of a curation process as is claimed. Rather, the "error-checking" in this claim is drawn to employing specific error-checking cells that contain special probes. As described on page 27, paragraph [0224] of Rothberg et al., error-checking cells and their associated probes are "designed to confirm that a signal observed from a particular cell in the primary observation array is in fact due to hybridization with the probe and not to an artifact."

Further, both paragraph [0069] and [0226], cited by the Examiner in making this

rejection, are drawn to describing such error-checking cells/sections on an array.

Given the discussion above, it is clear that the error checking described in Rothenberg et al. is drawn to the inclusion of specially designed probes on an array that are employed for quality control purposes. The error-checking of Rothberg et al. is carried out during the use and analysis steps of an array experiment and not during the design process as is claimed. As such, the Appellants submit that the error-checking taught in Rothenberg et al. does not teach or even suggest the curating error-checking step of Claim 47.

Because the error-checking of Rothenberg et al. is not drawn to curating a sequence of interest to find errors prior to selecting probes for that sequence, the Apellants submit that this reference fails to teach or suggest the missing subject matter in Zhou et al. Reversal of this rejection is thus respectfully requested.

Group II: Claim 49

As noted above, Claim 49 specifies that the curating step includes removal of any artifacts associated with a sequence assembly for the gene of interest identified by a user. The Appellants again note that curating a sequence as claimed is part of the probe selection/array design process and not drawn to array use and analysis steps.

In rejecting Claim 49, the Examiner asserts that Rothberg et al. teaches artifact removal associated with sequence assembly as claimed in Claim 49. To support this assertion, the Examiner cites Claim 15 and paragraphs [0026], [0029], [0147] and [0224] of Rothberg et al.

Claim 15 of Rothberg et al. reads as follows:

15. The method of claim 13 further comprising, before said detecting step, a step of washing said probe molecules hybridized with said second nucleic acid fragments at a stringency to remove mis-hybridized or non-specifically bound second nucleic acid fragments.

As is clear from above, Claim 15 is not drawn to removing sequence artifacts during sequence assembly but rather removal of mis-hybridized and non-specifically

bound nucleic acids during an array hybridization experiment: Further, paragraphs [0026], [0029], [0147] and [0224] all describe ways of physically manipulating samples before, during or after array hybridization to increase specificity and/or reduce background of the assays described therein. None of these sections are drawn to removing artifacts associated with sequence assembly (e.g., sequences assembled from multiple sequences in a database) as part of a curating step prior to selecting probes for the sequence.

Given the discussion above, it is clear that the artifact removal step taught in Rothberg et al. is drawn to the physical removal of unwanted or mis-hybridized nucleic acids during an array assay. The artifact removal disclosed in Rothberg et al. is not drawn to a curating step prior to selecting probes during an array design process as is claimed. As such, the Appellants submit that the artifact removal taught in Rothenberg et al. does not teach or even suggest the curating artifact removal step of Claim 47.

Because the artifact removal of Rothenberg et al. is not drawn to removal of artifacts from a sequence assembly for the gene of interest during an array design process, the Apellants submit that this teaching fails to remedy the deficiencies in Zhou et al. in making Claim 49 obvious. Reversal of this rejection is thus respectfully requested.

In summary, the Appellants submit that, for the reasons argued above, the combined teachings of Zhou et al. and Rothenberg et al. fail to teach of suggest each and every element of Claims 47 and 49 of the claimed invention and therefore cannot render these claims obvious. Reversal of this rejection is thus respectfully requested.

SUMMARY

I. Claims 1-22, 22, 27-28, 31-37, 41-46 and 48 are not anticipated under 35 U.S.C. § 102(e) over Zhou because the cited references fail to teach or suggest each and every element as set forth in the claims of the subject applications.

First, Zhou fails to teach curating a sequence for a user/customer-identified gene of interest followed by selection of probes for the curated sequence, an element of all of the claims appealed herein.

With regard to the claims of Group II, Zhou further fails to teach that the array design is completed by the user/customer (and not the vendor).

With regard to the claims of Group III, Zhou further fails to teach that the user/customer selects array layout parameters for the array design.

With regard to the claims of Group IV, Zhou further fails to teach that curating includes checking the sequence for errors, removal of commonly repeated subsequences, and/or removal of any artifacts associated with sequence assembly.

II. Claims 47 and 49 are not unpatentable under 35 U.S.C. § 103(a) over Zhou et al. (US 2003/0120432) in view of Rothberg et al. (2003/0003463).

Rothenberg et al. fails to remedy the deficiencies in Zhou et al. in teaching the elements of Claims 47 (Group I) and 49 (Group II).

Specifically, Rothenberg fails to teach 1) that the curating step includes checking the sequence of a gene identified by a user for sequence errors (Claim 47); and 2) that the curating step includes removal of any artifacts associated with a sequence assembly for the gene of interest identified by a user (Claim 49).

RELIEF REQUESTED

The Appellants respectfully request that the rejections of Claims 1-22, 22, 27-28, 31-37, 41-46 and 48 under 35 U.S.C. § 102(e) and Claims 47 and 49 under 35 U.S.C. § 103(a) be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

By:

Respectfully submitted,

Date: <u>June 26, 2007</u>

David C. Scherer, Ph.D. Registration No. 56,993

Date: <u>June 26, 2007</u>

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CLAIMS APPENDIX

1. A method for array design, comprising:

- (a) selecting, by a customer, at least one array design parameter and at least one gene of interest;
- (b) providing said at least one customer selected array design parameter and said at least one gene of interest to a vendor;
- (c) curating, by said vendor, a sequence for said at least one gene of interest:
- (d) selecting, by said vendor, at least one probe specific for said curated sequence;
- (e) providing, by said vendor, at least one additional array design parameter; and
- (f) completing at least one array design using said at least one customer selected array design parameter, said at least one vendor selected probe, and said at least one vendor provided array design parameter.
- 2. The method of claim 1, wherein said completing is carried out by said vendor.
- 3. The method of claim 1, wherein said completing is carried out by said customer.
- 4. The method of claim 1, wherein said array design is for a nucleic acid array.
- 5. The method of claim 1, wherein said at least one customer selected array design parameter comprises layout parameters.
- 6. The method of claim 1, wherein said at least one customer selected array design parameter comprises probe parameters.

7. The method of claim 1, wherein said at least one customer selected array design parameter comprises control probe parameters.

- 8. The method of claim 1, further comprising generating a visual interface for said customer, said visual interface providing a display with parameter selection options for said selecting.
- 9. The method of claim 8, wherein said generating said visual interface further comprises generating a visual display of an array layout for said customer, which visual display includes said at least one customer selected array design parameter.
- 10. The method of claim 9, further comprising reviewing, by said customer, said at least one customer selected array design parameter, as shown on said visual display of said array layout.
- 11. The method of claim 9, further comprising revising, by said customer, said at least one customer selected array design parameter.
 - 22. A gene-based array design system, comprising:
- (a) means for selecting, by an array customer, at least one gene of interest:
- (b) means for providing said at least one customer selected gene of interest to a vendor:
- (c) means for curating, by said vendor, sequence information for said at least one customer selected gene of interest;
- (d) means for selecting, by said vendor, a plurality of nucleic acid probes specific for said customer selected gene of interest; and
- (e) means for completing at least one array design that includes at least one of said vendor selected nucleic acid probes specific for said customer selected gene of interest.

27. A method for gene-based array design, comprising:

- (a) selecting, by a customer, at least one gene of interest;
- (b) providing said at least one customer selected gene of interest to a vendor;
- (c) curating, by said vendor, sequence information for said at least one customer selected gene of interest;
- (d) selecting, by said vendor, a plurality of nucleic acid probes specific for said at least one customer selected gene of interest; and
- (e) completing at least one array design that includes at least one of said vendor selected nucleic acid probes specific for said at least one customer selected gene of interest.
- 28. The method of claim 27, further comprising fabricating said at least one designed array.
- 31. The method of claim 27, wherein said completing is carried out by said vendor.
- 32. The method of claim 27, wherein said completing is carried out by said customer.
- 33. The method of claim 27, further comprising selecting, by said customer, other array design parameters.
- 34. The method of claim 33, wherein said other customer selected array design parameters comprise layout parameters.
- 35. The method of claim 33, wherein said other customer selected array design parameters comprise probe parameters.

Atty Dkt. No.: 10011076-1

USSN: 10/087,035

36. The method of claim 33, wherein said other customer selected array design parameters comprise control probe parameters.

- 37. The method of claim 27, further comprising generating a visual interface for said customer, said visual interface providing a display with parameter selection options for said selecting.
- 41. The method of claim 28, wherein said array fabrication is in-situ array fabrication.
- 42. The method of Claim 1, wherein said curating comprises checking the sequence for errors, removal of commonly repeated subsequences, and/or removal of any artifacts associated with sequence assembly.
- 43. The method of Claim 22, wherein said curating comprises checking the sequence for errors, removal of commonly repeated subsequences, and/or removal of any artifacts associated with sequence assembly.
- 44. The method of Claim 27, wherein said curating comprises checking the sequence for errors, removal of commonly repeated subsequences, and/or removal of any artifacts associated with sequence assembly.
- 46. The method of Claim 1, wherein said curating comprises checking the sequence for errors, removal of commonly repeated subsequences, and/or removal of any artifacts associated with sequence assembly.
- 47. The method of Claim 1, wherein said curating comprises checking the sequence for errors.
- 48. The method of Claim 1, wherein said curating comprises said removal of commonly repeated subsequences.

49. The method of Claim 1, wherein said curating comprises removal of any artifacts associated with sequence assembly.

EVIDENCE APPENDIX

Exhibit A: 37 C.F.R. § 1.131 Declaration of Robert Kincaid.

Exhibit B: Provisional Application 60/310,298

Atty Dkt. No.: 10011076-1

USSN: 10/087,035

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.

EXHIBIT A

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Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Application Number	10/087,035
Attorney Docket Number	10011076-1
Fäing Date	February 27, 2002
First Named Inventor	Robert Kincaid
Examiner	Carolyn Smith
Group Art	1631
Title	Arrey design system and methods

This Declaration and the attached Exhibit are being submitted in conjunction with the Applicants' Response to the Office Action dated September 21, 2004.

I, Robert Kincaid, do hereby declare as follows.

I am the inventor of the invention claimed in the above captioned application.

I have been asked to declare and provide factual evidence in support of conception of systems and methods for gene-based array design before July 16, 2001.

As evidenced by Exhibit A, I conceived of the systems and methods for genebased array design prior to July 16, 2001. The dates have been redacted from Exhibit A. All redacted dates are prior to July 16, 2001.

Exhibit A consists of photocopies of the Invention Disclosure (total of 6 pages) in which details of the gene-based array design systems and methods are described.

Pages 1 and 2 of Exhibit A are internal Invention Disclosure forms used by the Legal Department of Agilent Technologies. Pages 3-6 of Exhibit A describe the details of the first conception of the systems and methods for gene-based array design. In brief, a customer requests an array design from a vendor by providing at least one gene of interest. The vendor uses this information to

6.

7.

design probes specific for the gene (or genes) of interest as well as a design for the array. This invention removes the significant burden of probe and array design from the customer when requesting custom arrays.

The evidence provided in Exhibit A establishes that I conceived of genebased array design prior to July 16, 2001.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Respectfully submitted,

Date: 1/19/05

Robert Kincaid

Attachments: Exhibit A





1	S AND THE	P INVENTION	DISCLOSURE		PAGE ONE OF
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Gene-based arr	ay design	•	•		
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Name of Project	t: Life Science Inform	atics/Bioscience Information Sol	utions Department/SSL		
Product Name of	or Number: N/A				
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Signature Telnet Mailstop
(If more than four inventors, include additional information on another copy of this form and attach to this document)

Entity & Lab Name

Employee No.

					
S I INVENTION DISCLOSURE	,	·	AGE OF		
Signature of Witness(es): (Please try to obtain the signature of the The invention was first explained to, and understood by, me	ne person(s) to whom inve	ention was first disclosed.)	. 1	-	in and
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Matthew Yoshikawa	Muyo o	Mu		·	<u>·</u>
Inventor & Home Address Information: (If more than four inventor's Full Name	entors, include addl. inform	nation on a copy of this for	m & attach to this docum	nent)	
Robert Kincaid				`.	
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Half Moon Bay			California	24p 94019	
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Overview of Invention

This disclosure describes a novel approach for allowing microarray customers to design their own custom oligonucleotide arrays. Traditionally, array design is probe-centric and most of the effort goes into selecting the best probes to detect the genetic sequence of interest. In contrast, this invention decouples probe selection from the array layout process. Essentially, it proposes a tool that performs all array design functions except probe selection. With this tool, a customer can specify a design with respect to the intended targets, and probe selection is deferred to the manufacturer.

NOTE for simplicity this disclosure will simply refer to arrays or microarrays, but it should be understood to refer to *custom oligonucleotide arrays*. Also, for simplicity, the term gene is used to refer to the target nucleic acid for which a oligonucleotide probe is to be designed. This may actually be any nucleic acid target: genomic sequence, an mRNA, a single exon, etc.

Prior solutions and their disadvantages

Prior solutions to designing microarrays, center on selecting the best possible oligonucleotide probes. This usually requires using fairly complicated and specialized computational techniques. These computations as well as the sequence curation that precedes them are generally too technical and burdensome for average customers. Also, the process is very computationally intensive and may required expensive, specialized computing hardware/software. For this reason, customer design of arrays is generally viewed as problematic and unsupportable (from a commercial standpoint). To date the solution to this difficulty is to do all array design (including layout) within Agilent, while consulting with the customer on their requirements.

Problems solved by the invention

This invention simplifies array design both for the customer and for the microarray manufacturer by decoupling probe selection from array layout.

Advantages of the invention over what has been done before

This invention isolates the customer from the burden of sequence curation and probe selection computations, while still offering them the ability to personally select the appropriate layout and design choices for their custom array. In particular they can specify:

- 1 probe lengths
 - 2. control probe sequences (from a set of standard sequences)
 - 3. control probe layouts
 - 4. number of probes per gene
 - 5. inclusion/exclusion of deletion controls
 - layout patterns .
 - 7. precise position of probes on the array (with respect to the genes they represent)
 - 8. Number of features and density of array
 - 9. Number of probes per gene vs. replicate probes
 - 10. etc.

Further, it is anticipated that as microarray technology progresses, most interesting genes will have well established probe sequences and the computational aspects of probe selection will no longer be necessary. When this happens, the transition from probe computation/selection to probe lookup is straightforward. The customer tool is not involved in this process and does not care how the probe was actually selected (computation vs. lookup). Once a sufficient catalog of good probes has been collected, a future version of the customer design tool *could* include specific probe selection.

Another advantage of this invention is that it permits the array customer to visually adjust their array layout on-site, and see precisely what the layout will look like. This avoids complications and errors in communication between Agilent application scientists and the customer, during the process of defining the customer's requirements for the array.

Description of the construction and operation of the invention

Essentially, the invention would consist of a software program with a user interface that could be either a stand-alone program or a web-based application. The user interface would allow the specification of all required layout parameters. It would further include a user-supplied *gene* specification (vs. a *probe* specification) for each non-control feature on the array.

This gene-centric array design would be ovided to Agilent (or any array manufacture). The specified genes would be extracted from the design. Based on how many replicates are specified, the number or probes per gene is determined. From this information the actual sequence curation and probe selection can take place as usual. The resulting probes can then be laid out in the user-specified pattern.

Below are rough schematic diagrams showing how current array designs are handled (Fig. 1), how we traditionally viewed customer software for array design (Fig. 2), and how this invention proposes to decouple probe selection from array design (Fig. 3).

Figure 1. Current Array Design Workflow

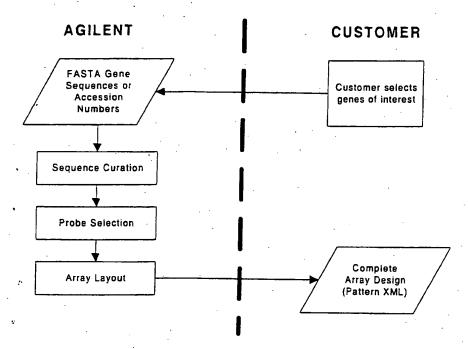
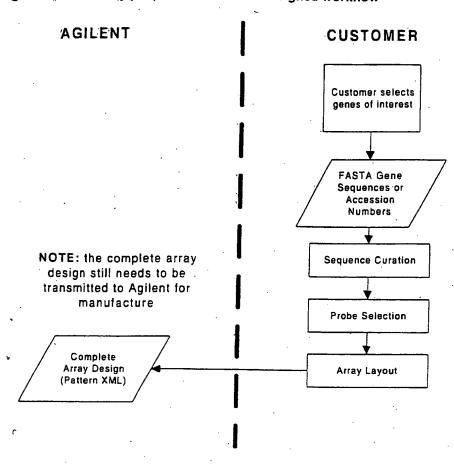


Figure 2. Previously proposed custo r-designed workflow





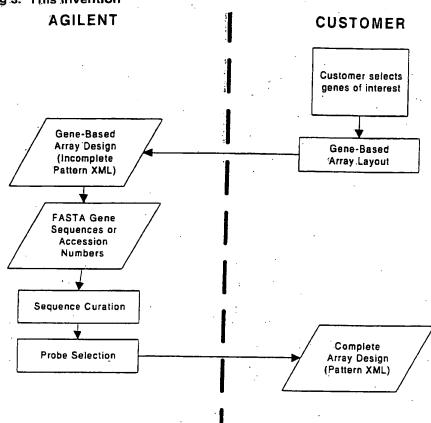


EXHIBIT B



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PTO/SB/16 (8-00)

Approved for use through 10/31/2002. OMB 0651-0032
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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)								
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The invention was made by an agency of the United States Government or under a contract with an agency of								
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TYPED or PRINTED NAME Wei Zhou (if appropriate)								
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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiatry is governed by 35 U S C 122 and 37 CFR 1.14 This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U S Patent and Trademark Office, U.S Department of Commerce, Washington, D C, 20231 DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS SEND TO Box Provisional Application, Assistant Commissioner for Patents, Washington, D C 20231

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for FY 2001	Filing Date	6/25/01	
•	First Named Inventor	Zhou	
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Name (Print/Type)	Wei Zhou	Registration No. Attorney/Agent)	44,419	Telephone	408-731-5000
Signature	11/	524		Date	6-25-2061

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In the United States Patent and Trademark Office

A Provisional Patent Application

Web Application for Designing and Ordering Flexible Content Arrays

Inventor: Xuemei Zhou

Assignee:

Affymetrix, Inc.

3380 Central Expressway Santa Clara, CA 95051

1 INTRODUCTION

The Software Requirements Specification (SRS) will outline the requirements and functional characteristics of the Flexible Content Software, Version 1.0. The Flexible Content Software will perform the following two functions:

- Provide an interface for an external/internal customer to request a Flexible Content Array Design through the Internet. This is the Flexible Content Array designer (FCA) application.
- Provide an interface for a chip designer to perform a Subset design based on the information a customer submitted online. This is the SubsetDesign application.

1.1 Purpose

The purpose of this requirement specification is to define the system level requirements for the Flexible Content Software. The system level requirements include a description of the components, features, functions and interface requirements.

1.2 Scope

The intended audience of this document includes the following groups:

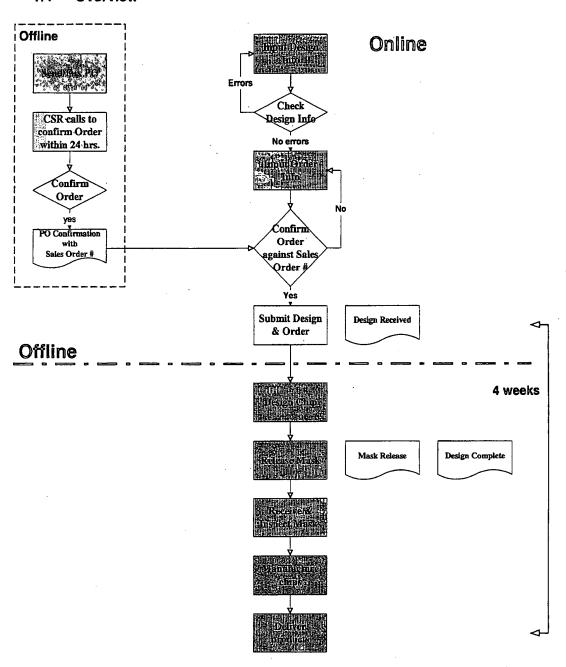
- Software Engineering
- Software Test
- Marketing
- Quality Assurance

1.3 Definitions, Acronyms, and Abbreviations

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Custom Design	The design of an expression array based on
	sequences and instructions provided by a customer.
Subset Design	The design of an expression array based on probe
	sets from existing designs.
Flexible Content	Designs with a tight turn-around time of 4 weeks or
Design	less using an offset mask strategy. Initially, this will
	only include subset designs, but can later be
	expanded to include designs that include a mixture of
	subset and custom designs.
CSR	Customer Service Representative
PO	Purchase Order
SO#	Sales Order number stored in Affymetrix QAD
Chip Orders	The centralized email box for Chip Design.
CDD	Chip Design Database, where ALL chip design related
	information is stored.
EASImart	Database mart used to stored array design
	information; shared with the Matrix (Portal) project.

FCdb	Flexible Content Database, used to stored all data used to support the online portion of the Flexible Content application.
T&Cs	Terms and Conditions

1.4 Overview



The process flow for a Flexible Content Design is designed to mirror that of the current Custom Design process. The online Flexible Content Array designer (FCA) portion is new, which is to ensure that a user will have an easier time putting together a design request, and that the design information is correct as they come into Chip Design. Since this is a quick turn-around design, it is essential that the data are correct when they come in, so that no

time will be wasted on correcting the Design Request. All currencies currently supported by Affymetrix will be supported by the FCA application. The currency is set based on the customer's billing address.

In order to guarantee that the online order is valid, a manual offline process is still used to qualify the Purchase Order. The Purchasing Agent from the requestor's company must send Affymetrix a PO detailing the design request fee and the number of chips to purchase. Affymetrix CSR will confirm the order and generate a Sales Order number in QAD. The SO# will be communicated to Chip Design and the Purchasing Agent, as well as the requestor. Chip Design will input the SO# into FCdb, and the customer is required to put in the same SO# for their design request. The web application will then check the SO# against FCdb. Only with this valid SO#, the requestor will be able to complete the design request online. This manual process is put in place to make sure that time will not be lost because the PO is not valid.

The second part of the process, SubsetDesign, is offline, and is handled by Chip Design. The process will be just like a current Custom Design, so that we can make sure all hand-offs are handled correctly. We have four weeks to deliver the products to the customer's site from the time a design comes in.

There are three key milestones during the Chip Design process. At each milestone, an email message will be sent to the relevant recipient to communicate the status of the design.

- PO Confirmation: when a CSR confirms the PO with the requestor/purchasing agent, an email is sent to Chip Orders with the SO#. The same SO# is also communicated to the requestor/purchasing agent so that the requestor can use the SO# to complete his/her online design request.
- Design Received: when a requestor completes the FCA correctly, an email message is sent out to the Requestor, Customer Service, Chip Design, and Purchasing. The 4-week countdown starts from here. If Purchasing wants to assign a different mask vendor other than the default used for Flexible Content designs, they notify Chip Design upon receipt of this email message.
- 3. Mask Order Form / Mask Release / Design Complete: when the design is complete, Chip Design sends out "Mask Order Form" to the mask supplier, "Mask Release" to internal Affymetrix departments, and "Design Complete" message to the external requestor. The mask data go out to the mask supplier at this point.

1.5 Reference

CSOP AX028: Probe Array Design Request Process

DOP AC004: Chip Design Process

2 GENERAL DESCRIPTION

2.1 Product Perspective

The Flexible Content Software, Version 1.0, will provide the mechanism for a chip designer to perform a Flexible Content Design based on customer specifications. The software will support design data specifying a set of probe sets from existing designs.

The software will analyze the customer's design data and generate an array to the specifications. Front-end support (online) will allow the user to produce, check and order a Flexible Content Design online. The back-end (offline) software will generate the files required for manufacturing and analysis.

2.2 Product Functions

2.2.1 Flexible Content Array designer (FCA)

The Flexible Content Array designer (FCA) is the online application that will guide a user to produce a Design Request for a Flexible Content Array design. It will also allow more advanced users to upload a list of probe sets they have already created. The application will then check to make sure that the content and syntax are correct. If that is the case, it will guide the user through the ordering process and notify the correct parties of a new design by sending a "Design Received – Due Date Set" message to Chip Orders and the requestor. Chip Orders will automatically forward this message to the appropriate internal Affymetrix departments, including CSR, Materials and Manufacturing. Based on the array information received, a Chip Designer can log on to the application and download the correct design into a local driver for processing.

2.2.2 SubsetDesign

The SubsetDesign (offline) application will take the Subset Request File from the FCA application and the related design information to produce a set of output files. These output files will be used with the existing Chip Design software to do the mask design and to generate the library files for analysis.

2.3 General Constraints, Assumptions and Dependencies

2.3.1 Standards

To ensure comparable quality from array to array, the following standards are enforced on ALL Flexible Content Designs:

- the format of the mask will be 100/9 to begin with; other formats will become available later
- default mask material: Quartz
- o default mask supplier: Photo Sciences

- 75 synthesis steps
- antisense designs only
- 20 micron feature size
- probe sets derived from TIGR sequences will NOT be available
- 4 QC arrays from each wafer will not be sent to customers. These four arrays contain specific QC control probes.
- o controls on each array:
 - 1. Corner checkerboard
 - 2. Spaced normalization controls: 6 x 6 grid
 - 3. Text: the array name supplied by the customer will be the text shown on the array. The array name can be up eight characters long.
 - 4. All Chips controls in a standard block, not distributed: bioB, bioC, bioD, cre
 - 5. All Chips controls: dap, lys, phe, thr, trp
 - Constitutively expressed controls: for each different species
 where the probe sets come from, the following species-specific
 controls will be tiled on the chip. If duplicated control(s) have
 already been selected in the customer's list, the duplicates will
 be eliminated.
 - > Arabidopsis: actin 3, 5, M; gapdh 3, 5, M
 - > Drosophila: actin 3, 5, M_f, M_r; gapdh 3, 5, M
 - Human:

actin 3, 5, M; gapdh 3, 5, M

Mouse:

actin 3, 5, M; gapdh 3, 5, M

➤ Rat:

actin 3, 5, M; gapdh 3, 5, M

➤ Yeast:

actin 3, 5, M

2.3.2 Constraints

- The first phase implementation will NOT include sequence blasting capabilities when a search is performed.
- Design requests will NOT go directly into the CDD in the first phase implementation.
- Subset designs will NOT be produced directly from the CDD, nor FCdb in the first phase implementation.
- The web browsers supported will be Internet Explorer 4.0 or higher, and Netscape Communicator 4.5 or higher.

2.3.3 Dependencies

- The Portal project will provide the sequence blasting capabilities the Flexible Content needs. Tighter integration will be necessary to make the communication between the two applications seamless in a later phase.
- FCdb will extract array-related information from the EASImart.

- The backend SubsetDesign will use released Analysis Files for input, instead of the database. It is assumed that EASImart and the Analysis Files will contain consistent information.
- The new probe selection rules will dictate the final design of a new CDD. Once the new CDD is loaded with data, the Flexible Content software will be inputting the Design Request directly into the database, and exporting the final manufacturing and analysis files directly from the database.

3 USER SCENARIOS

3.1 Invalid Browser

If the user accesses the Flexible Content site using a browser not supported by the application (Netscape 4.5 or higher, Internet Explorer 4.0 or higher), the user will be warned. Links for Netscape Navigator and Microsoft Internet Explorer are also provided.

3.2 New User

When a user access the Flexible Content site without a valid user ID and/or password, he/she may sign up following the registration process for the Portal. A user qualified as "customer/partner" by the Portal will automatically gain access to Flexible Content. However, if billing and/or shipping addresses are missing for that particular user, the user will be directed to update the profile first.

3.3 Login and Order

Once logged in, a user has two ways to start a design request. First, upload a file containing a list of desired probe sets (from past experiments and/or various searches performed using Affymetrix tools). If the file format is not correct, error(s) will be displayed. It will also show link to the file description for a Probe Set File. Once uploaded, the data in the file will be checked against FCdb. If a probe set cannot be located, it will be deleted from the list, and the user will be notified of the deletion. If a probe set can be located, but for a different design than the one indicated, the information will be shown to the user, and he/she may elect to add it to the list. If a probe set can be located in more than one design (using the probe set name as the only criterion), all designs with the same probe set name will be listed. Alternatively, if the user provides the same probe set name multiple times, this duplicated error will also show up. The user may elect just one set, or elect multiple sets by giving a distinct name to each set selected.

The second way is to perform a search and select the desirable probe sets returned by the query. The user must provide at least one criterion in order to search. When multiple criteria are selected, the query will search ALL or ANY of those criteria against FCdb. The query results will be displayed but not

selected. The user may select one or more probe sets returned and add them to the design request.

The file load and searches can also be combined. Species specific controls will be added to the design request based on the probe sets selected. If these controls have already been selected by the user, then they will NOT be duplicated.

At all time during the design request, the maximum number of available probe pairs will be shown. The total number of probe pairs selected will be updated continuously. The application will alert the user if the total goes over the maximum. The user will NOT be able to complete the order if the total is over the maximum.

The user must provide an array name and description for each design request. This custom array name can be up to 8 alphanumeric characters long. The official array name (used by Affymetrix) will be generated by adding a two-letter customer specific code to the beginning of the custom array name, and a one letter code "F" (to denote fast track). The official array name will be checked against the database to make sure it is unique.

In order to proceed with the order, a user must put in a SO#. This SO# is generated offline by the CSR, and must be obtained before the order can go through. This SO# is checked against the database to make sure it is valid.

Once the user enters the number of arrays ordered, the total order will be calculated and shown. This amount is only an **estimate**. The final invoice will be based on the number of actual chips shipped to the requestor. The currency used will be based on the billing address.

At any time BEFORE the completion of the order, the user may view and/or save all the probe sets selected for a particular design request. The file saved will be in a tab-delimited text file format. They may also save a copy of a mock PO showing the array name, description, and order amount for the design request. This mock PO will be in a HTML/text format.

Before the final confirmation for the order, the user will be shown the info for design request. Once confirmed, an email notification will go out to Chip Design and the requestor. It will be automatically forwarded to CSR, Materials and Manufacturing. A Chip Designer can download the correct design by logging on and provide the array name and file path.

3.4 Logout without Ordering

When a user logs out without ordering, the request will be treated as an incomplete order.

3.5 Incomplete Orders

When a user logs in, if there are incomplete order(s) associated with that user, the orders will be shown. The user may choose to work on one of them at a time, work on a new request, or to purge them all from the database.

3.6 Feedback

Feedback will be incorporated through the Portal.

3.7 Support

Contact information for support will be combined with the contact for the Portal.

4 FLEXIBLE CONTENT ARRAY DESIGNER (FCA)

4.1 Security

The web application will be hosted on a secured server. All users are required to login before they can access the site to start a design. The user login function will be shared with the Portal project. In addition, each page has a specific access level. When accessing, the user's access level will be checked against that of the web page to make sure that the user has the right to view a particular page. The access rights are shared with the Portal project.

4.2 Page Description

4.2.1 Browser Check

Before accessing the Flexible Content home site, the user's browser will be checked by the application. If the Browser used is not Netscape Communicator 4.5 or higher, or Internet Explorer 4.0 or higher, the user will be warned. The user may click on the links to download the supported browsers.

4.2.2 Flexible Content Home

The Home page displays any Incomplete Orders, as well as providing a mean for users to start working on a new design. If the billing and/or shipping addresses are missing, the user will be redirected to the Profile page to add the required information.

For a new request, the array name and array description must be provided. The array name is up to 8 characters long (alphanumeric plus hyphens). A two-letter company code prefix and "F" suffix will be added to this array name to make the official array name. This official name will be checked against the database for uniqueness. If it is not unique, the user will be alerted to enter a new name. This official array

name will also be the text on the array. The array description is limited to 255 characters long.

4.2.3 FAQ

This page shows the FAQ's for Flexible Content.

4.2.4 Tutorials

This page contains tutorials for Flexible Content.

4.2.5 Contact

This page is shared with the Portal, and shows the contact information for Flexible Content related help.

4.2.6 Privacy Policy

This page contains the Affymetrix Privacy Statements regarding user information collected online. It is shared with the Portal project.

4.2.7 Terms & Conditions

This page contains the standard Terms and Conditions that a customer has signed when registering for the online use.

4.2.8 Feedback

This page is incorporate through the Portal project.

4.2.9 Register

This page allows a new user to sign up online for a new user id and password. This process is handled by the Portal project.

4.2.10 Login

This page allows a user to log in. This function is shared with the Portal.

4.2.11 Upload Probe Set File

This page allows a user to load a tab delimited text file containing probe set information.

4.2.12 Invalid File

This page appears if the Probe Set File loaded cannot be processed correctly. The error message will point the user to the instructions on how to prepare a Probe Set File.

4.2.13 Probe Set Not Found

This page shows any probe sets in the Probe Set File that cannot be found in the database. These probe sets will not be added to the design request.

4.2.14 Probe Set Misidentified

This page shows any probe sets in the Probe Set File that can be found, but not for the array specified. The correct information is shown for these probe sets, and the user may elect to add one or more of these probe sets to the design request.

4.2.15 Duplicated Probe Set

This page shows any duplicated probe sets in the Design Request without a unique name, or cannot be identified uniquely in the database by the information given. For example, if someone enters probe set "12345_at" multiple times, even if this probe set occurs only once in the database, it is a duplicate. On the other hand, if someone enters a probe set "3857_at" only once in the database without any additional information, and there are three probe sets in FCdb matching that name, this will also be treated as a duplicate.

4.2.16 Probe Set List

This page lists the probe set information. It has two states:

- Verified probe sets loaded from the Probe Set File all the probe sets are shown as selected. A user may deselect one or more probe sets from the design.
- Summary of what has been saved as the design so far this is activated through clicking on the "View Design" button in the Navigator page, or through the Modify Design button in various pages. All the probe sets are just like those loaded from the Probe Set File.

4.2.17 Probe Set List - search results

This page lists the query results from the Search page – all the probe sets shown are not selected. A user may select one or more probe sets to add to the design.

4.2.18 Search

This page allows the user to search the available arrays by the following criteria to come up with a design:

- Array description / Array name
- Part number
- Probe set name (inexact match, case-insensitive)
- Key word(s) in probe set description (inexact match, caseinsensitive)
- Public database identifier (exact match, case insensitive)

Array description/array name fields is a multi-selection list. The user may specify to query ALL or ANY of the criteria entered. In the future,

this page will integrate with the Portal to allow users to search by blasting sequences also.

4.2.19 Order

This page shows the general summary of the design. It allows a user to enter the relevant order information before submitting the order to Affymetrix. The currency shown will be based on the user's billing address. In order to complete the ordering process, the user must obtain a valid Sales Order number before the design submission. This Sales Order number is generated by Affymetrix Customer Service, and is entered into the FCdb manually once the CSR approves the PO. In the future, this Sales Order number should be automatically obtained from the QAD in real time.

This page also allows the user to modify their array name and descriptions, as well as modifying the probe sets in the design.

4.2.20 Invalid Sales Order

This page shows the error messages related to the Sales Order:

- 1) Order without any actual probes in the design request
- 2) Order with too many probes than the space allowed
- 3) sales order number not found
- 4) total order amount exceeds the PO approved

4.2.21 Order Verification

This page shows ALL information related to the design request one last time, including the PO, billing and shipping addresses, as well as probe sets info in the design request. It also warns the user that once submitted, this design request cannot be modified or canceled.

If the user is not happy with the probe sets at this point, he/she can hit the "Modify Design" button and make additional changes.

4.2.22 Order Confirmation

This page confirms the successful submission of the Flexible Content design. An email message will be automatically sent out to the requestor and Chip Design with the order information, with "Design Received – Due Date Set" as part of the subject. The email will be forwarded to internal Affymetrix departments automatically, including CSR, Materials, and Manufacturing.

4.2.23 Incomplete Orders

This info is shown on the Main page, as well as the Order Confirmation page. It shows all the incomplete orders associated with a particular user. It allows the user to pick one design to work on at a time, to start

a completely new design, or to purge all the design related information currently in the database. A warning will appear before proceeding to ask the user to confirm if he/she really wants to erase ALL existing orders.

4.2.24 Design Info

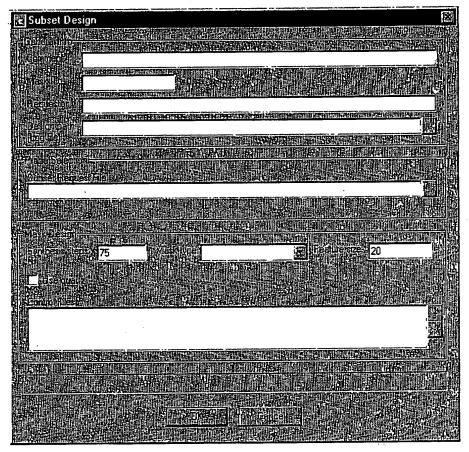
This info is shown on the Upload, Search, Probe Set List, Probe Set List-Search, Order, and Order Verification pages. It shows the maximum number of probes allowed, and keeps a tally of the running total of probes in the design request.

4.2.25 Chip Design Download

This page allows a chip designer to go online and download the subset request file for an array.

5 SUBSETDESIGN

5.1 User Interface Requirements



5.2 Security

Access to the SubsetDesign application is only available to Chip Design in Affymetrix.

5.3 Functionality

The Subset Design application has the following fields:

Field Name	Field Type	Description
Comment	Text	Any comment for the design
Mask ID	Text	Mask ID assigned by the Chip Designer. The application will access the availableMasks.txt file, find the corresponding Mask ID, and read in the Array Name, Array Description and Part Number. The Array Name will be used as the text on the array.

Field Name	Field Type	Description
Requestor	Text	Name and company of the
		requestor. This information will be
		written as part of the output in the <aut> file, as an input to Maiar.</aut>
Design Path	Text	The file path of the design where
Design Fall	I GAL	all the output files will be stored.
		The general path is:
		Q:\alldes\cdesign\ <companycode< td=""></companycode<>
·		> <mask id=""></mask>
Subset Request File	Text	The Instruction File outputted by
		the FCA application.
Synthesis steps	Text	Number of synthesis steps to
		produce the design. The default is
		75. This is the standard for all current Subset designs.
Mook han	Selection	The format of the mask. The
Mask type	Selection	current choices are 100/9 and
		400/4. The current option for
		Subset designs is only 100/9.
Feature size	Text	The feature size for the design.
		The default is 20 micron.
Use quartz	Checkbox	The mask material. When
		checked, Quartz is used; when
		unchecked, Soda Lime is used.
Control Files	Multi-selection	Additional controls to be tiled on the array. The two AllChips
,		controls will be added
		automatically. Species specific
		controls will be added by the Chip
		Designer.
OK	Button	Checks the Subset Request File.
		If everything is okay, write the
		output files to the Design Path.
Cancel	Button	Cancels the execution.

5.3.1 Design Checks

The checking performed by the application includes the following:

- The array name is correct, and the associated Analysis Files exist. DataPaths.txt contains a list of all the existing designs and the file path for their associated Analysis Files.
- The probe sets listed can be found in the Analysis Files for the array design listed.

- Probe set names are unique; or, if there are duplicated probe set names, a "Rename" column exists to give unique names for all probe sets to be tiled onto the array.
- If "Rename" is used, the last three characters (suffix denoting the target strandedness of the probe set) are the same as that of the original probe set name.
- Additional controls to be tiled onto the array. If there are duplicated controls in the Subset Request File, then the duplicates will be eliminated (but not the renamed duplicate controls).

5.3.2 Design Output

5.3.2.1 <AUT> File

Input to Maiar, the application that starts the mask design process. It contains information about the requestor, array name, description, part number, and synthesis direction.

By default, all designs are to be synthesized in the reverse direction. If a design contains only sense probe sets, then it will be synthesized in the forward direction. In the case of a mixed design (where there are both sense and antisense probe sets), the sense probe sets will be tiled on reverse-complemented and synthesized in the reverse direction (using the "orientedExp" command).

The <AUT> file produced will point to the correct mask template for a subset design, which includes a mini-design for QC chips. QC controls (bioB, bioC, bioD, cre) are to be put in a box at a fixed location in every array. These probes are NOT to be distributed. All other probes on the array will be distributed as normal. CheckMask application will be run twice for every design. It checks the normal arrays that will be sent to the customer, as well as the mini-QC arrays.

The text on the array will be the **array name** produced by Affymetrix. It contains the name supplied by the requestor, which is up to 8 characters long. The official array name (used by Affymetrix) appends a 2-letter code in front (which is company specific), and a 1-letter code at the end of the original name "F", which denotes fast track. For example, an antisense design from Roche with the original name as "Test1" will have the official name as "roTest1F". The text on the array will be "roTest1F".

5.3.2.2 <IIN> File Linked to the <AUT> file. The <IIN> file is the input to the CreateChip application.

5.3.2.3 (PRB) Probe File List of all the probes corresponding to the probe sets requested in the Subset Request File.

5.3.2.4 Sequence File Sequences corresponding to the probe sets listed in the Probe File in FASTA format.

5.3.2.5 Instruction File Instructions corresponding to the Sequence File. The Sequence File and Instruction File are produced so that they can be used to generate the Analysis Files with the current LibFiles application.

6 APPENDIX

6.1 Flexible Content Database

The Flexible Content Database (FCdb) is designed to support functionality through Phase III. Please refer to the Flexible Content Database documentation for detail (FCdb_db2.doc)

6.2 Initial Offerings

YG-S98

There are 23 eukaryotic catalog designs available for the Phase I launch.

•	AtGenome1	Arabidopsis Genome Array
	DrosGenome1	Drosophila Genome Array
•	HG-U95Av2	Human Genome U95Av2 Array
•	HG-U95B-E	Human Genome B-E Arrays
•	Hu35KsubA-D	Human 35K A-D Arrays
•	HuGeneFl	HuGeneFl Array

HuGeneFL Array

MG-U74Av2-Cv2 Murine Genome U74 Av2, Bv2, Cv2 Arrays
 Mu11KsubA-B Murine 11K A-B Arrays
 RN-U34 Rat Neurology U34 Array
 RG-U34A-C Rat Genome U34 Arrays
 RT-U34 Rat Toxicology Array

Yeast Genome S98 Array

6.3 Probe Set File

The Probe Set File contains the following columns:

- 1. ProbeSetName: the name of the probe set
- 2. ArrayName: the name of the array design where the probe set comes from
- 3. ArrayDescription: the description of the array design
- 4. PartNumber: the part number of the array
- 5. Rename: if a probe set name is duplicated in a design, a new name must be assigned to the duplicated item using the value in this column. If two probe sets are duplicated, only the second one needs a value in "rename".

The only mandatory column is ProbeSetName. This is basically a Subset Request File if all the data is correct. It will be the input to the FCA application. All probe sets listed will be checked by the application. It will get turned into a Subset Request File as an output.

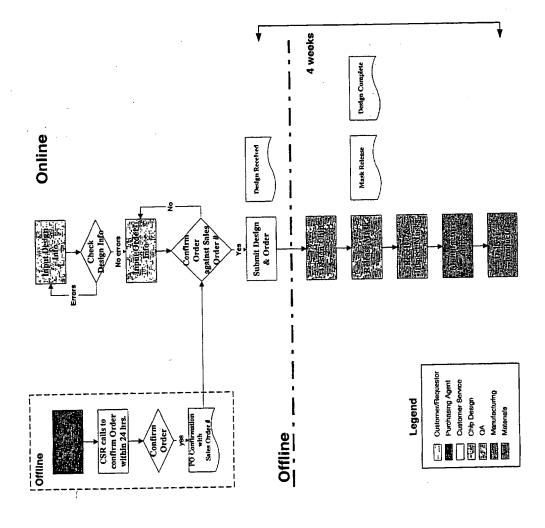
6.4 Subset Request File

The Subset Request File contain the following tab-delimited columns:

- 1. ProbeSetName
- 2. ArrayName
- 3. Rename

ProbeSetName and ArrayName are mandatory. Rename is only mandatory when there are duplicated probe set names in the ProbeSetName column.

Business Process Flow



Software Design Requirements

➣ Online Error Checking

- Secured Work Environment
- Upload Design Request File
- Create Request Online
- TIGR Probe Sets Not Available
- Save Validated File
- Mandatory Controls
- Error Checking Without Ordering

Software Design Requirements

- continued

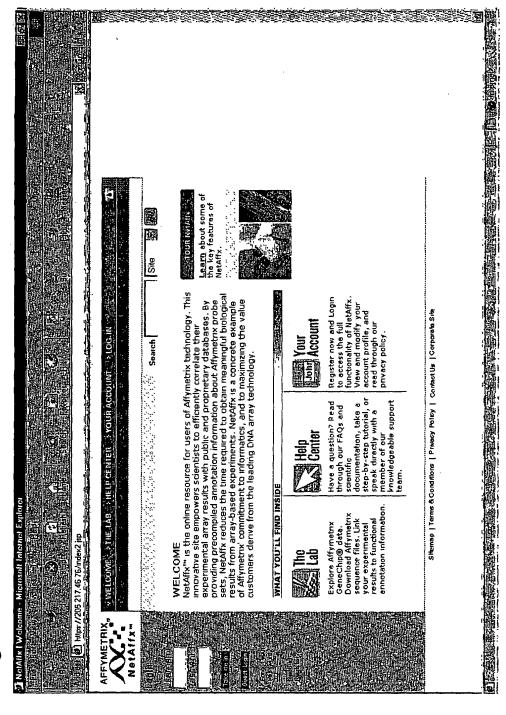
✓ Online Ordering

- Display Order Info
- Support Foreign Currencies
- Email Notification

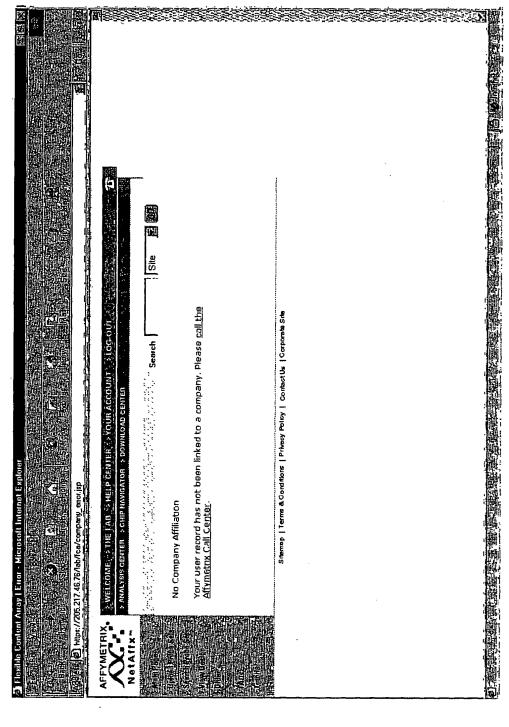
✓ Offline Chip Design

Perform Chip Design Quickly and Accurately

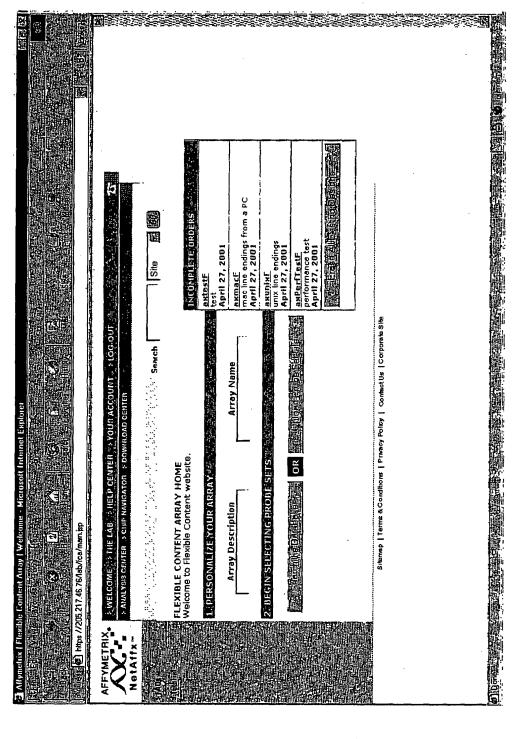
Login



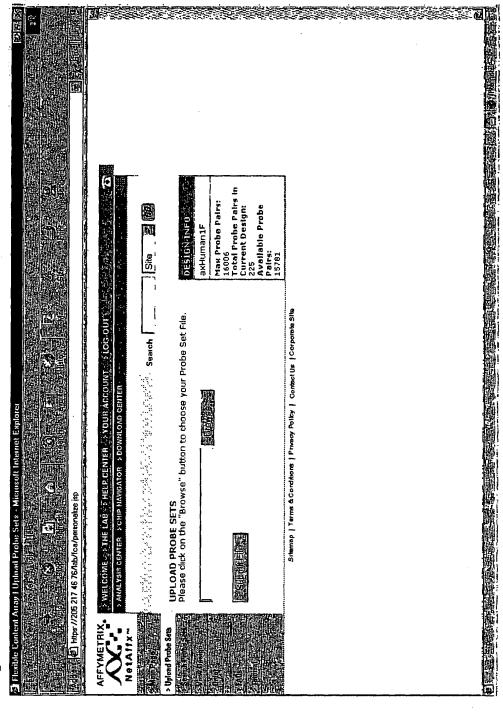
Login Error



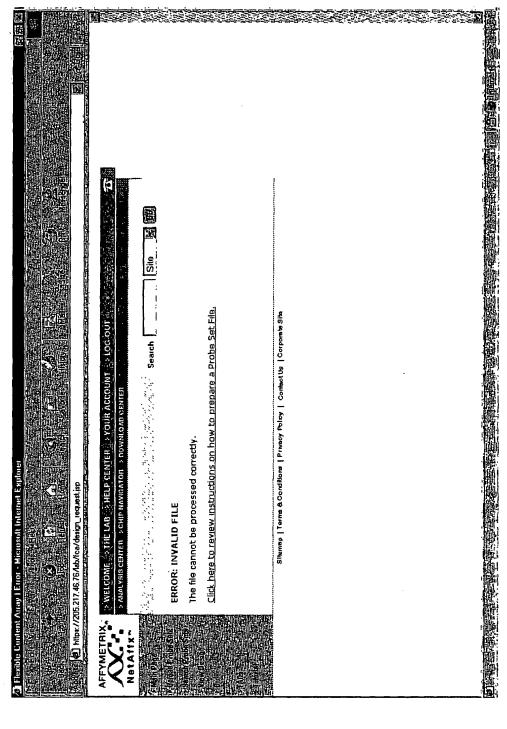
FCA Home



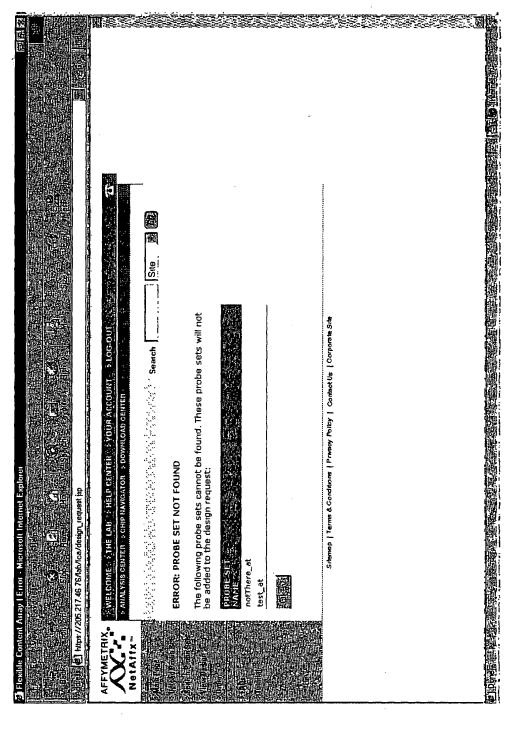
Upload



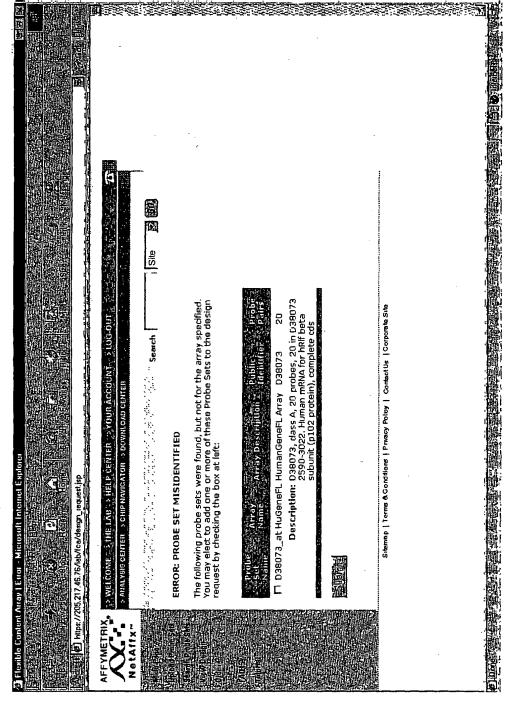
Error - Invalid File



Error -Not Found



Error - Misidentified



Error - Duplicated

	#Flexible Content Atray Littor • Microsoft Internet Explorer	
Adding 0 Htps://205	Ntys://205 217.46.76/ab/fca/design_request,isp	
Miller Car	a La Caracia Caracia Caracia Caracia Caracia Search Sille	
British Politisher	The following probe sets do not have unique names. Each probe set in your design request must have a unique name. Please select just one of each dunloated another of the problem. Please select just one	
	Alternatively, you can provide a new name in the "Rename" field for a duplicated probe set. You must still select such a renamed probe set	
	using the checking them. by not checking them.	
	Probe Set Name Array Description Rename Public m probe Name	
	l¹ 40276_at HG- Human Genome U95Av2	
	Description: Cluster Ind. D50063:Human mRNA for proteasome subunit p40_/ Mov34 protein, complete cds /cds=	
	ģ	
	1 40276_at	
	Description: Cluster Incl. D50063:Human mRNA for proteasome subunit p40_/ Mov34 protein, complete cds /cds=	
	(83,1057) /gb=D50063 /gi=971269 /ug=Hs.155543 /len=1602 /STRA=for	
	T. U73142_g_at RN-U34 Rat Neurobiology U34	
	Description: U73142 Rattus norvegicus p38 mitogen activated protein kinase mRNA, complete cds /cds=	
	(11,1093)/gb-U73142/q=1621646/uq-Rn.3293/len=3132	
	7) U73142_g_at U34A Rat Genome U34A Array 15	
	Description: U73142 Rattus norvegicus p38 mitogen activated protein kinase mRNA, complete cds /cds=	
	(11,1093)/gb=U73142/gi=1621646/ug=Rn.3293/len=3132	
	17 U73142_g_at RT-U34 Rat Toxicology U34 Array	
	Description: U73142 Rattus norvegicus p38 mitogen activated protein kinase mRNA, complete cds /cds=	
	111.1000.101.1000.101.101.101.101.101.1	

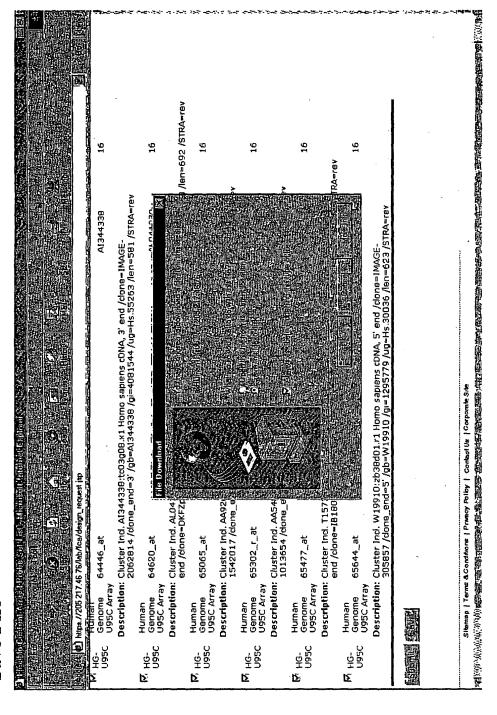
Probe Set List

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IST robe Sets shown from the design request becked Probe Sets Probleman Indian AFEX HSACO7/X00351_3_at Probleman Uman AFEX HSACO7/X00351_A_at 20 Uman AFEX HSACO7/X00351_A_at 20 Uman AFEX HUMGAPDH/M33197_3_at 20 Uman AFEX HUMGAPDH/M33197_A_at 20 Inschiption: U38480 /FEATURE = /DEFINITION=HSU38480 Human retunoid x receptor-damma mRNA, complete 20 Anschiption: U38480 /FEATURE = des /DEFINITION=HSONHORE H.sapiens mRNA for orphan nuclear hormone 16 Anschiption: U38480 /FEATURE = des /DEFINITION=HSONHORE H.sapiens mRNA for orphan nuclear hormone 16		The second second second	Search		
Trope Sets shown from the design request Trope Sets shown from the design request Publisher	PROBE SE	T LIST		,	
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					Max Probe Pairs: 16006
Control Human AFFX-HSAC07/X00351_3_at 20 Control Human AFFX-HSAC07/X00351_A_at 20 Control Human AFFX-HUMGAPDH/M33197_3_at 20 Control Human AFFX-HUMGAPDH/M33197_A_at 20 Control Human AFFX-HUMGAPDH/M33197_A_at 20 Control Human AFFX-HUMGAPDH/M33197_A_at 20 Human AFFX-HUMGAPDH/M33197_A_at 20 Horan Horan 20 Horan AFFX-HUMGAPDH/M33197_A_at 20 OSSAY2 USSAY2 AFFX-HUMGAPDH/M33197_A_at 20 Human 20 230428 16 Human 230425 16 USSAY2 USSAY2 230425 16 Description: 20425 /FEATURE=cds /DEFINITION=HSONHORE H.sapiens mRNA for orphan nuclear hormone 16	Array	Array Description	Probe Set Noname Identifier	Probe	Total Probe Pairs Current Design: 15955
Control Human AFFX-HSAC07/X00351_S_at Control Human AFFX-HUMGAPDH/M33197_3_at Control Human AFFX-HUMGAPDH/M33197_A_at Control Human AFFX-HUMGAPDH/M33197_M_at Luman HWB Genome U95Av2 U95Av2 1048_at Luman Human Human AFFX-HUMGAPDH/M33197_M_at Luman U95Av2 U95Av2 Array Cds /5TRA=for Human Human Homan AFFX-HUMGAPDH/M33197_M_at Human Cds /5TRA=for Human Array Hose Genome Cds /5TRA=for 230425 Array Array Description: 230425 /FEATURE=cds /DEFINITION=HSONHORE H.sapiens mRNA for orphan nuclear hormone	Contro	I Human	AFFX-HSAC07/X00351_3_at	20	Availabie Probe Pairs: 51
Control Human AFFX-HSAC07/X00351_M_at Control Human AFFX-HUMGAPDH/M33197_3_at Control Human AFFX-HUMGAPDH/M33197_M_at Lontrol Human AFFX-HUMGAPDH/M33197_M_at Human HG- Genome U95Av2 U95Av2 1048_at VATAY Description: U38480 /FEATURE= / DEFINITION=HSU38480 Human retinoid X receptor-qamma mRNA, complete cds / STRA=for HG- Genome GS / STRA=for HG- Genome L05_at Array Description: 230425 /FEATURE=cds / DEFINITION=HSONHORE H.sapiens mRNA for orphan nuclear hormone	Contra	Human	AFFX-HSAC07/X00351_5_at	20	
Control Human AFEX-HUMGAPDH/M33197_3_at Control Human AFEX-HUMGAPDH/M33197_A_at Control Human AFEX-HUMGAPDH/M33197_A_at Human Howard Hosav2 U95Av2 105Av2 Array Description: U38480 /FEATURE = /DEFINITION = HSU38480 Human retunoid X receptor-gamma mRNA, complete cds /STRA=for Human Human HG- Genome cds /STRA=for 230425 Human Array HG- Genome cds /STRA=for 230425 HG- Genome cds /STRA=for 230425	Contro	Human	AFFX-HSAC07/X00351_M_at	20	
Control Human AFFX-HUMGAPDH/M33197_S_at Control Human AFFX-HUMGAPDH/M33197_M_at Ho- Genome U95Av2 U95Av2 Array Description: U38480 /FEATURE / DEFINITION=HSU38480 Human retinoid X receptor-gamma mRNA, complete cds /STRA=for Human AFFX-HUMGAPDH/M33197_M_at Description: U38480 /FEATURE / DEFINITION=HSU38480 Human retinoid X receptor-gamma mRNA, complete cds /STRA=for Human AFFX-HUMGAPDH/M33197_M_at Description: U38480 /FEATURE = / DEFINITION=HSU38480 Human retinoid X receptor-gamma mRNA, complete cds /STRA=for Human AFFX-HUMGAPDH/M33197_M_at Description: U38480 / STRA=for Ho- Ges / STRA=for Array Description: Z30425 / FEATURE = cds / DEFINITION=HSONHORE H.sapiens mRNA for orphan nuclear hormone Description: Z30425 / FEATURE = cds / DEFINITION=HSONHORE H.sapiens mRNA for orphan nuclear hormone	Contra	II Human	AFFX-HUMGAPDH/M33197_3_at	20	
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HUMBAN HG-GBROME U95Av2 U95Av2 LU38480 Description: U38480 /FEATURE= /DEFINITION=HSU38480 Human retinoid X receptor-gamma mRNA, complete cds /5TRA=for Human HG-GBROME U95Av2 U9	Contro	J. Human	AFFX-HUMGAPDH/M33197_M_at	20	
Description: U38480 /FEATURE = /DEFINITION=HSU38480 Human retunoid X receptor-gamma mRNA, complete cds /STRA=for Human retunoid X receptor-gamma mRNA, complete cds /STRA=for Human retunoid X receptor-gamma mRNA, complete cds /STRA=for Bescription: Z30425 /FEATURE=cds /DEFINITION=HSONHORE H.sapiens mRNA for orphan nuclear hormone persontor /STRA=for		Human Genome 2 U95Av2 Array	1048_at		
Human HG-Genome 105_at U9SAvZ U9SAvZ Array Description: 230425 /FEATURE=cds /DEFINITION~HSONHORE H.sapiens mRNA for orphan nudear hormone		Description:	U38480 /FEATURE= /DEFINITION=HSU38480 Human retinoid X receptor-gamma mRNA, cds /STRA=for	complete	
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		Description:	230425 /FEATURE=cds /DEFINITION=HSONHORE H.sapiens mRNA for orphan nudear h receptor /STRA=for	ormone	

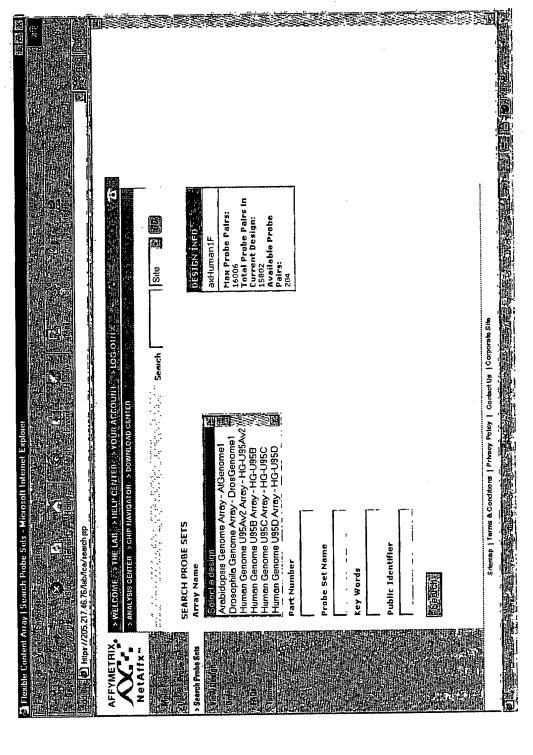
Probe Set List

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β̈́	Human		;
095C	Genome U95C Array	6462U_at	16
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НG- U95С	Human Genome U95C Array	65065_at AA926703	16
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HG- U95C	Human Genome U95C Array	65302_r_at	16
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区 HG- U95C	Human Genome U95C Array	65477_at	16
	Description:	ion: Cluster ind. T15735:181809 Homo sapiens cDNA, 3' end /clone=181809 /clone_end~3' /gb=T15735 /gi~517897 /ug=Hs.169760 /len=584 /STRA=rev	4=rev
i⊏]HG- U95C	Human Genome U95C Array	65644_at W19910	16
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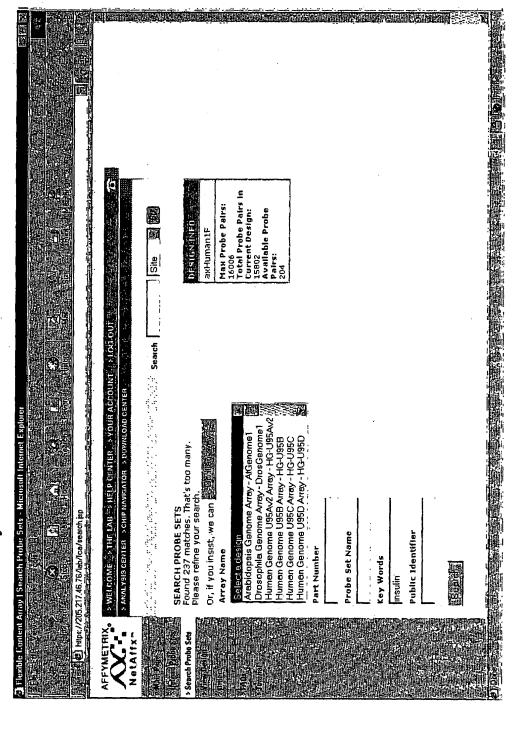
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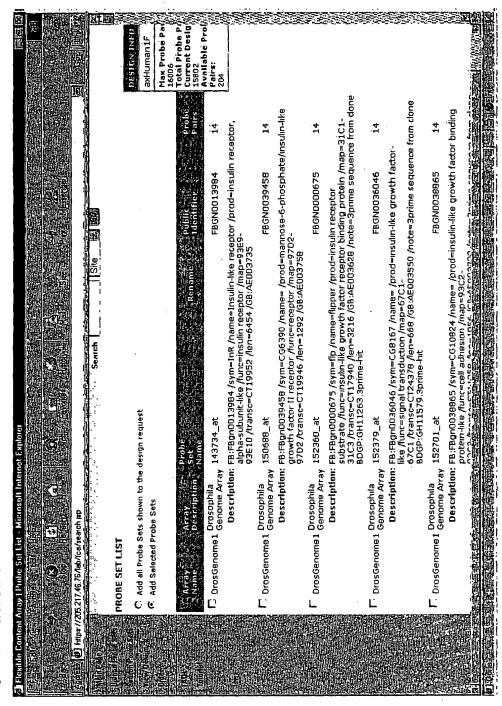
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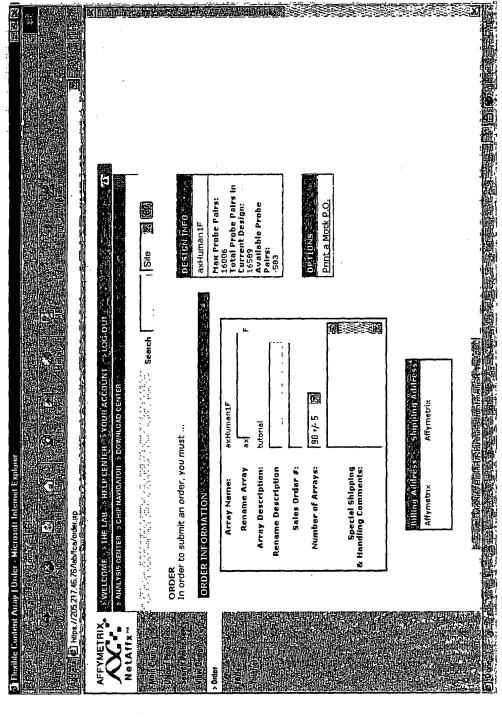
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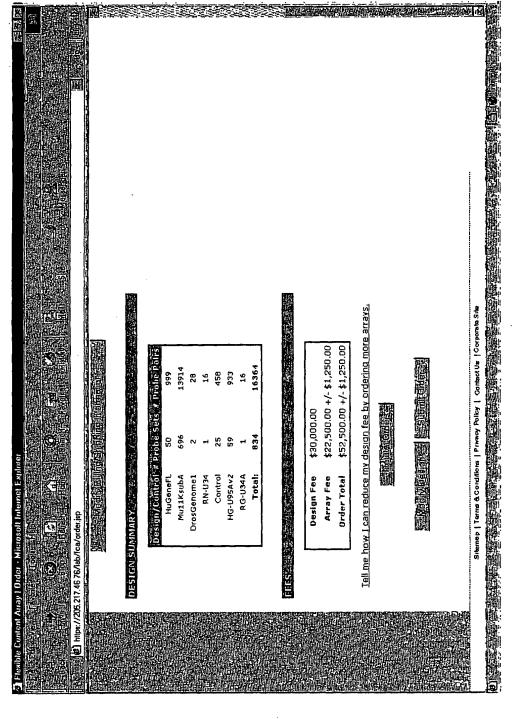
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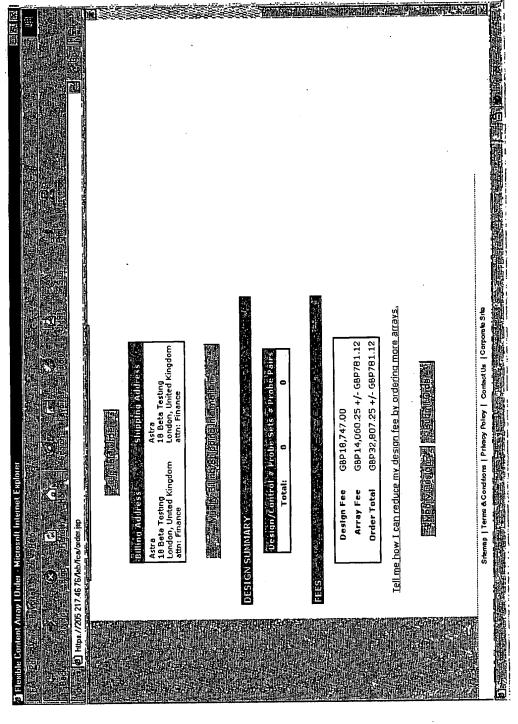
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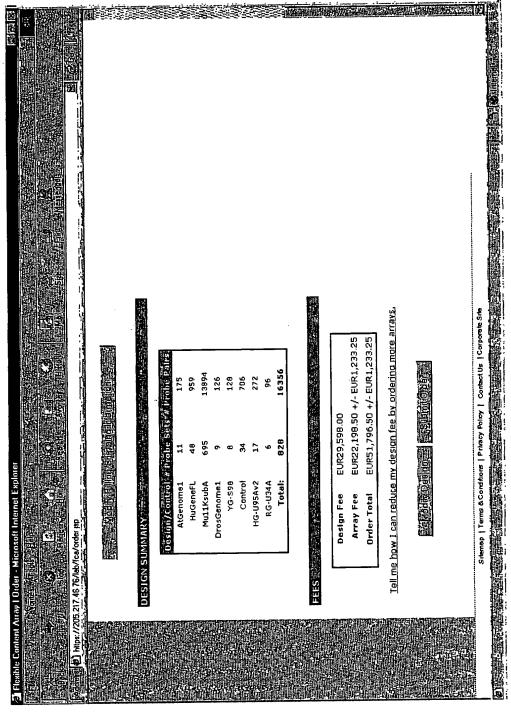
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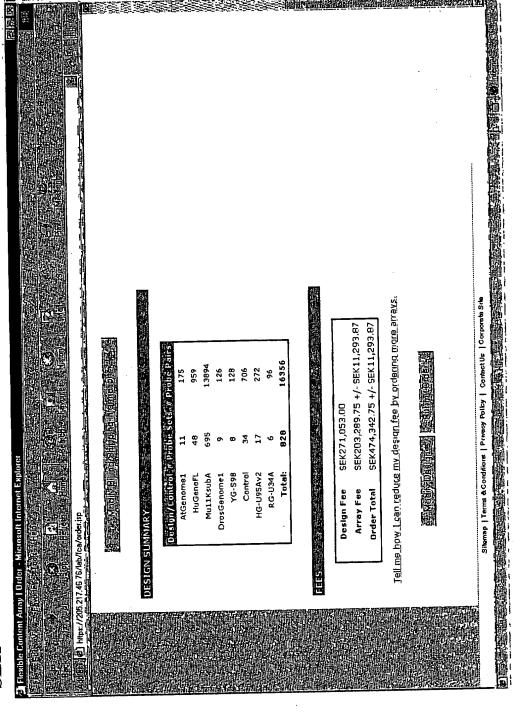


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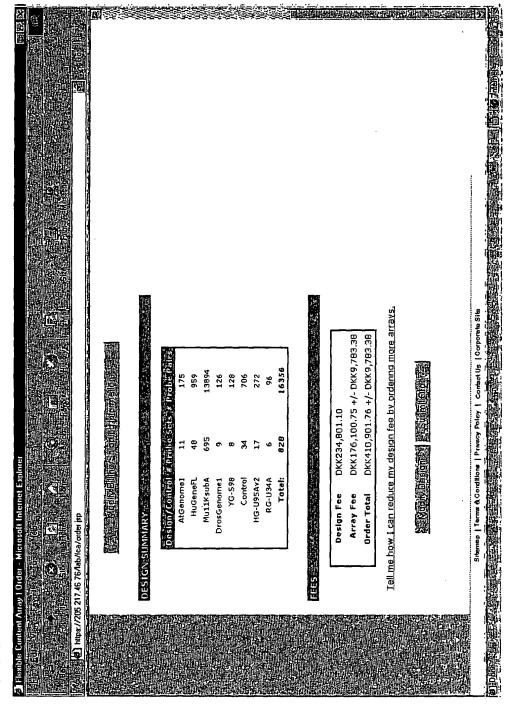


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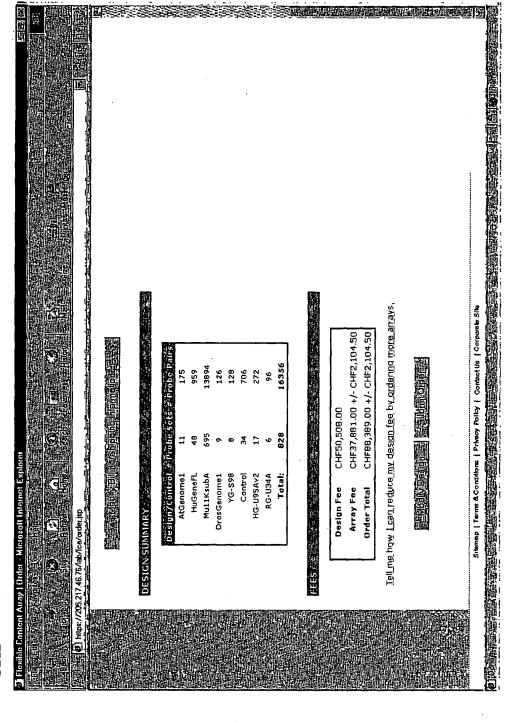




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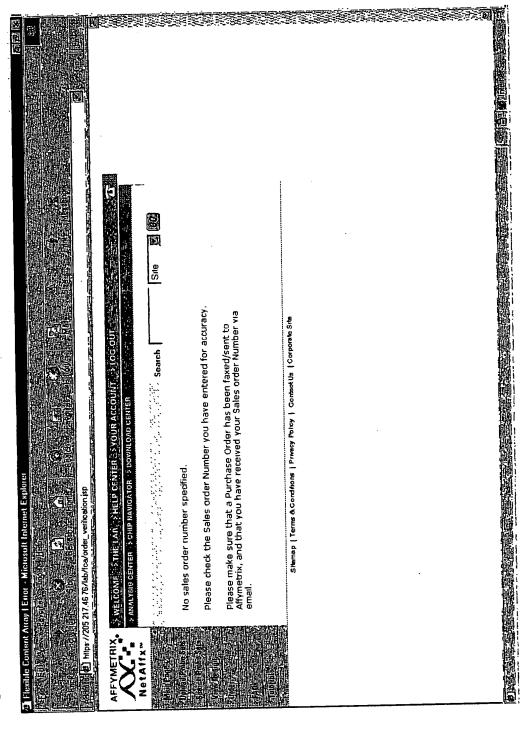
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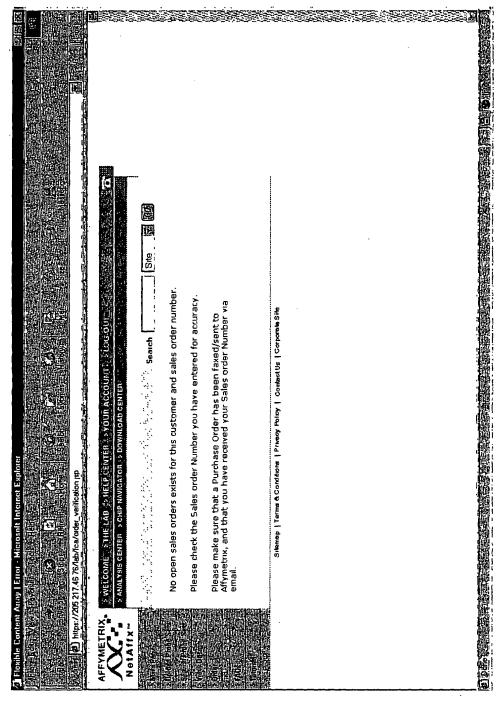
Mock PO

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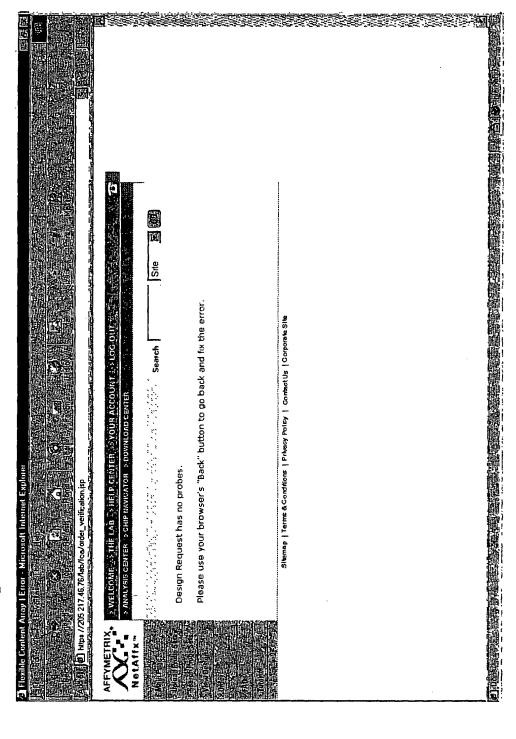
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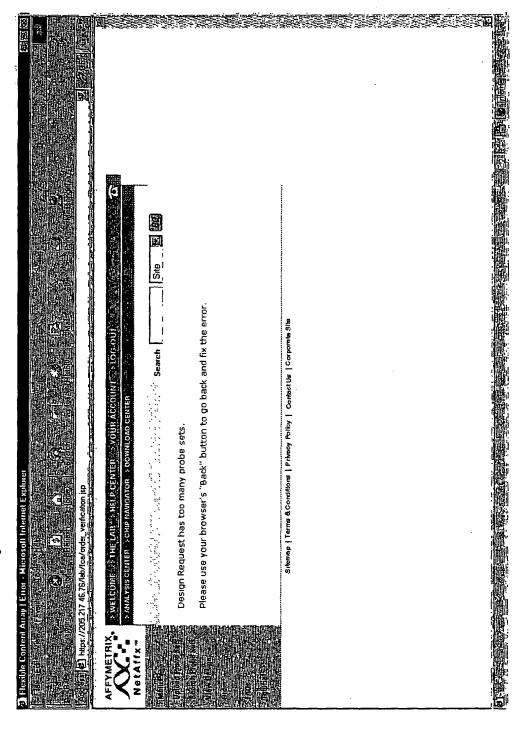
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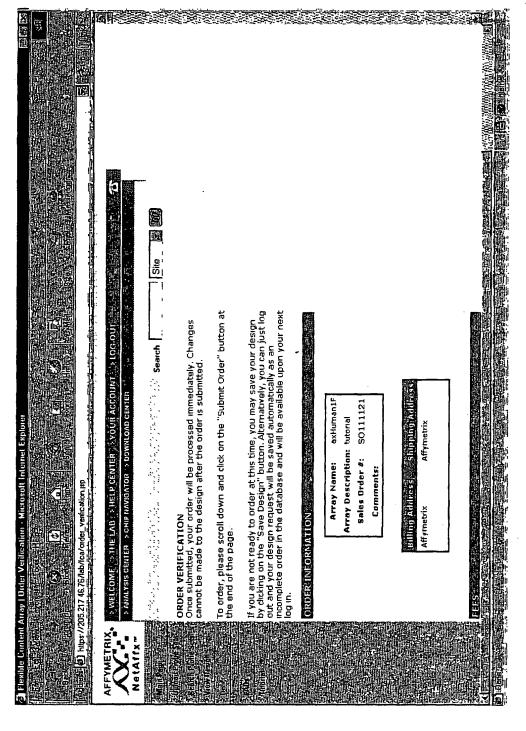
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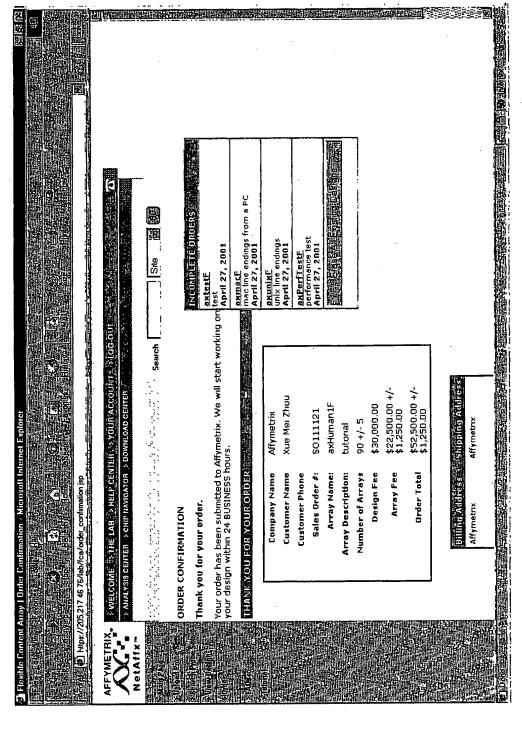


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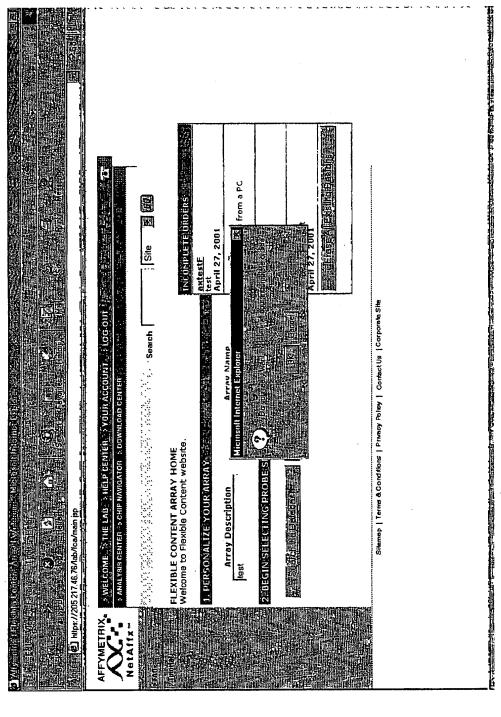


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